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Do Not Throw Away Your Patient's Shot at Complete Vomiting Control

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ABBREVIATIONS CIV, chemotherapy-induced vomiting; CINV, chemotherapy-induced nausea and vomiting

KEYWORDS chemotherapy-induced vomiting; chemotherapy-induced nausea; antiemetics; clinical practice guidelines

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Introduction

During the early days of chemotherapy, chemotherapy-induced nausea and vomiting (CINV) was considered manageable when chemotherapy could continue with receipt of intravenous hydration. Not surprisingly, CINV was the treatment-related adverse effect most dreaded by patients. Today, nausea and vomiting are repeatedly identified by pediatric cancer patients as among the top 5 most bothersome symptoms they experience.[1–3] However, recent pediatric trials report rates of complete chemotherapy-induced vomiting control of 79% to 92%[4–7] and clinical practice guidelines make strong recommendations that pediatric patients receive specific antiemetic prophylaxis known to be safe and effective.[8–10] Why the disconnect?

Four key steps to optimize a pediatric patient's chance at experiencing complete CINV control are as follows: (1) providing evidence-based CINV prophylaxis; (2) including dexamethasone and (fos)aprepitant in antiemetic regimens thoughtfully; (3) responding in timely and effective ways to treat breakthrough CINV; and (4) deprescribing medications given for antiemetic purposes for which there is little or no evidence of efficacy. These steps are discussed below.

Evidence-Based CINV Prophylaxis

We now have evidence-based recommendations from pediatric clinical practice guidelines to guide the selection of CINV prophylaxis[8,11] and the management of anticipatory,[9] breakthrough, and refractory[10] CINV. These recommendations have been endorsed by the Children's Oncology Group and the Multinational Association of Supportive Care of Cancer and have been adapted for use by many institutions internationally. They represent the international standard for chemotherapy-induced vomiting (CIV) prophylaxis for pediatric patients. Yet, implementation of these clinical practice guidelines is challenging and guideline-consistent prophylaxis is often not provided.[12]

In some instances, guideline-inconsistent prophylaxis may be reasonable. For example, a recommended antiemetic may not be licensed in a jurisdiction or, even when available, its off-label use as an antiemetic (eg, olanzapine) may not be permissible. A recommended antiemetic may be inappropriate for an individual patient because of allergy, history of adverse reaction, or concurrent conditions. However, when recommended agents are obtainable, their pediatric use is permissible and when there is no patient-specific contraindication for their use, pharmacists must advocate strongly for the implementation of guideline-consistent care. Advocacy may include arguments regarding the cost-efficiency of guideline-recommended antiemetics and the false economy of not including effective antiemetics, such as palonosetron, on the formulary. Incorporation of guideline-consistent antiemetic regimens into chemotherapy order sets is a commonly employed implementation tactic. However, tools such as care pathways, algorithms, educational modules, and posters will likely be required to change local practice and facilitate the delivery of evidence-based CINV prophylaxis. Pharmacists are often best placed to lead guideline-consistent CINV management implementation.

Dexamethasone and (Fos)Aprepitant Restrictions

Both dexamethasone and (fos)aprepitant are extremely effective antiemetics. Dexamethasone, when added to a first-generation 5-hydroxytryptamine-3 receptor antagonist, such as ondansetron or granisetron, increases the complete acute phase CINV control rate among patients receiving highly emetogenic chemotherapy substantially (RR 1.36, 95% CI, 1.23–1.50).[13] Similarly, neurokinin-I inhibitors such as (fos)aprepitant, when added to a 5-hydroxytryptamine-3 receptor antagonist and dexamethasone, significantly increase the complete acute phase CINV control rate among patients receiving highly emetogenic chemotherapy

(RR 1.07, 95% CI, 1.01–1.13).[13] However, dexamethasone is frequently withheld from chemotherapy-naïve pediatric patients for reasons that are not grounded in evidence, including concerns of wound healing and neutrophil recovery impairment. Conversely, although (fos)aprepitant can increase the dose intensity (area under the concentration vs time curve) of chemotherapy agents that are CYP3A4 substrates by 2- to 5-fold or reduce the CYP3A4-mediated activation of chemotherapy agents to their active form,[14] it is often given without regard to the potential resultant toxicities or reduced treatment efficacy. Ideally, the circumstances for the use of each agent would be based on a thoughtful evaluation of their risks and benefits and include the perspectives of patients or their representatives. Institutional standardization would permit iterative quality improvement.

Responsiveness to Breakthrough CINV

Without assessment, it is impossible to realize when a patient is experiencing breakthrough CINV and, thus, impossible to initiate a timely response. As a minimum practice standard, nurses should record the time hospitalized patients vomit or retch in the health record. Ideally, nausea severity would be assessed by inpatients and outpatients during the acute and delayed phases of each chemotherapy block using a validated pediatric patient-reported measure.[15,16] This information should also be recorded in the health record. Symptom screening measures such as SSPedi may also be used to flag patients with bothersome nausea or vomiting who may benefit from more focused evaluation.[1]

The availability of patient outcome data in the health record enables the creation of dashboards that inform clinicians of their patients' situation in real time and makes quality-improvement projects more manageable because data extraction from the electronic health record can be automated. For example, Walsh et al[17] have created a dashboard that displays each inpatient's chemotherapy and antiemetic regimen, the congruence of the antiemetic regimen with institutional CINV management policy, and the vomiting rate.

Modern adult and pediatric trials evaluating interventions to manage breakthrough CIV initiate the intervention when participating patients vomit once.[10] To repeat, the first vomit triggers an intervention. Pediatric clinicians, on the whole, are relaxed about vomiting and often seem to expect their patients to vomit: "It is bone marrow transplant conditioning, after all!" Because a history of vomiting is an important risk factor for future vomiting, it is important to intervene quickly and effectively when a patient vomits. Each patient should have a breakthrough CINV management plan that can be initiated when a patient vomits or experiences bothersome nausea despite prophylaxis. This management plan should include revisiting decisions to withhold dexamethasone or (fos)aprepitant because the risk:benefit equation will have shifted once the patient has experienced breakthrough CINV. The patient's experience with breakthrough CINV should be incorporated into the antiemetic selection for the next chemotherapy block so that refractory CINV can be prevented. This requires clear and accessible charting of antiemetic treatment plans in the health record.

Deprescribing Antiemetics

Before the availability of 5-HT3RA, metoclopramide, phenothiazines, diphenhydramine, and dimenhydrinate were commonly used to prevent CINV. Complete CIV control rates were dismally low. While metoclopramide continues to be recommended for specific pediatric patients with refractory CINV,[10] agents other than those recommended in current clinical practice guidelines may offer patients only potential toxicity with little or no efficacy. They may also introduce an opportunity cost because the initiation of effective antiemetics may be delayed, and the risk of future vomiting may therefore increase.

Institutional antiemetic practices may be deeply entrenched and difficult to shift. Pharmacists may undertake retrospective or prospective quality-improvement projects to understand how historical practices contribute to CIV control. Pharmacists undertaking such projects should publish their findings to benefit the larger community. An audit of CINV prophylaxis provided and feedback on patient outcomes to clinicians may be effective ways to improve complete CIV control rates.

In many institutions and jurisdictions, pharmacists prescribe antiemetic prophylaxis either independently or following a standardized rubric. Rather than following historical practices, pharmacists must advocate for evidence-based and experience-informed antiemetic practices, particularly when writing these orders.

In conclusion, it is our vision that all patients receiving cancer treatment will be free of vomiting, retching, and nausea and will maintain their usual appetite throughout therapy. To realize this vision, pharmacists must ensure that each of their patients enjoys the highest probability of complete CINV control starting with their very first chemotherapy block—that they do not throw away their patient's shot. This can be accomplished by delivering guideline-consistent care, responding quickly to breakthrough CINV, and avoiding ineffective and potentially unsafe interventions. However, gaps in our knowledge of CINV remain (eg, uncertainties regarding emetogenicity classification, antiemetic dosing, individual risk factors), and even with careful attention, some patients will not achieve complete CINV control. However, we can do better for our patients, even with the tools currently available.

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